REMARKS

Applicant wishes to thank the Examiner for the careful consideration given to this application.

In the Office Action, the Office rejected claims 27-31 and 33-35 under 35 U.S.C. §103(a) as being unpatentable over WO 00/64482 (*Olson*) in view of either Yick et al., Chondroitinase ABC Promotes Axonal Regeneration of Clarke's Neurons After Spinal Cord Injury, 11 NeuroReport 57, 1063-67 (*Yick*) or Zuo et al, Regeneration of Axons after Nerve Transection Repair is Enhanced by Degradation of Chondroitin Sulfate Proteoglycan, Experimental Neurology, vol. 176, 221-28 (*Zuo*). Additionally, the Office rejected claim 32 under 35 U.S.C. §103(a) as being unpatentable over *Olson* in view of either *Yick* or *Zuo* and further in view of U.S. Patent No. 5,262,522 (*Gearing*).

Upon entry of this Response, claims 27-35 will remain pending and claims 1-26 are canceled. For the reasons set forth below, Applicant requests that the rejections associated with the pending claims be withdrawn.

REJECTION OF CLAIMS 27-31 AND 33-35

Claims 27-31 and 33-35 are rejected under 35 U.S.C. § 103(a) as being obvious over *Olson* in view of *Yick* or *Zuo*. Applicant respectfully disagrees.

It cannot be obvious to destroy intended function of a reference such as Olson

Claim 27 is nonobvious over *Olson*, *Yick* and/or *Zuo*, either alone or in combination. The primary cited reference here is *Olson*. The asserted changes to *Olson*, along with the corresponding combinations with other art, would destroy the intended functions of the primary reference *Olson*. As discussed in greater detail below, *Olson* sets forth a particular approach for converting a growth-inhibiting site into a growth-promoting one.

Applicants respectfully submit that one skilled in the art would not combine the teachings of *Olson* with *Yick* or *Zuo* to obtain the claimed invention as this would destroy the advantage disclosed in *Olson*. See *Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1358-59 (Fed.

Cir. 2008) (stating that a claimed invention would not be obvious where modification of the prior art would destroy its advantageous property). In contrast to the Office's rationale, substituting the anti-end of the amphibody of *Olson* to obtain the claimed invention would destroy the intended purpose of *Olson*. See MPEP 2143.01(V). Olson teaches sequestration of the inhibitory molecule and simultaneous on-the-spot presentation of a stimulatory molecule. See *Olson* at pg. 19, lns. 20-26. Thus, the Office's substitution of the anti-end with the claimed polypeptide which degrades a nerve-growth inhibiting substance would destroy the intended purposes of *Olson* which include changing an inhibitory site into a stimulatory site and acting as a "molecular magnet" to direct nerve growth. See *Olson* at pg. 6, lns. 19-26.

Binding of the anti-inhibitory molecule to stimulatory molecules, the anchoring of stimulatory molecules at the formerly inhibitory site, and a directed pattern of growth rather than a random pattern of growth are requisite features of *Olson*. Each of these three requisite features of *Olson* would be destroyed by the asserted rejection. Moreover, the claim elements for which *Olson* is cited are not found in the remaining references. Accordingly, it is respectfully submitted that the elements of the claimed invention are not found in the prior art and that the rejection be withdrawn.

Requisite features of Olson

The intended subject matter of *Olson* has certain key aspects:

one, the sequestration of a growth-inhibiting region;

two, the change of this specific formerly inhibitory region into a growth-promoting one (at the same site); and,

three, a directed pattern rather than random nerve growth. See *Olson* at pg. 7, lns. 1-4 and pg. 9, lns. 5-14 and lns. 24-26.

In view of these features, rather than leading to a finding of obviousness under the statute, *Olson* actually discouraged a person of ordinary skill in the art at the time of the present invention from destroying the inhibitory region; conversely, destruction of an inhibitory region is both set forth and claimed in the present application. Because *Olson* emphasizes the importance of altering an

inhibitory region into a stimulatory one precisely at the spot of the inhibitory molecule, *Olson* teaches away from the present claimed invention. In particular, the claimed invention does not require turning an inhibitory region into a stimulatory region at precisely the same site but allows the polypeptide with growth-promoting activity and the polypeptide which degrades nerve growth-inhibiting molecule to act where each is needed, respectively. In contrast, *Olson* discourages this type of chimeric protein because it teaches that turning an inhibitory site into a stimulatory site is required.

I. Olson requires sequestration of a growth-inhibiting region.

The Office asserts that the anti-end of the chimeric protein of *Olson* is not restricted to antibodies and may include inhibitors/suppressors of chondroitin proteoglycans that have the function of suppressing or neutralizing a neurite growth inhibitory effect. Applicant respectfully disagrees. Rather than disclosing or suggesting such alternatives, it is a requisite disclosure of *Olson* that the "anti-" end of the amphibody must bind to inhibitory molecules in the tissue environment and thereby sequester these regions. See, e.g., *Olson* at pg. 4, lns. 10-16. However, even if the Office were not convinced that *Olson*'s disclosure is limited to antibodies, the need in *Olson* for antibody-type binding is reflected by *Olson*'s definition of "neutralizing" as "dock on and cap" thus even if the moiety were not an antibody the moiety must possess the kind of specific binding that antibodies possess in order to effectively "cap" the site. See *id.* at pg. 4, lns. 12-13[1]

II. Olson requires conversion of this specific formerly inhibitory region into a growth-promoting one.

The next fundamental aspect of *Olson* is that once the inhibitory region is sequestered with the *Olson* "amphibody," that former inhibitory region is then converted into a growth-promoting region. Again, an antibody moiety or a moiety with specific binding such as with antibodies is needed under *Olson* to achieve this conversion function. In fact, the amphibodies

[1] In contrast, the Office asserts that the chimeric protein of the present claims will function to localize the "pro-end" having neural growth stimulatory activity and converting an inhibitory site to a stimulatory site as taught by *Olson*. Although this may occur transiently, this ignores the overall teaching of the present invention which is to not merely bind to but to degrade inhibitory molecules.

of *Olson* are referred to as "molecular magnets wherein bipolar features have been fused together". *Olson* at pg. 4, lns. 16-18 and pg. 6, lns. 24-26.

Consistent with the requisite need in *Olson* to specifically bind to an inhibitory region and thereby alter its inhibitory properties, each method of manufacturing set forth therein is directed to the use of antibodies as the anti-end. See *id.* at pg. 20, lns. 28-31, FIG. 1, pg. 42, ln. 14 to pg. 46, ln. 26, pg. 47, lns. 25-29 (describing the design of the amphibody as incorporating three major parts: an antibody, a neurotrophic factor and a linker), and pg. 48, lns. 1-9. It is clear that *Olson* is not enabled for any inhibitors or suppressors other than antibodies/amphibody molecules. To see *Olson* otherwise, and thereby destroy its intended function, appears to interpret the need for a solution to a long-felt need (e.g., neural growth) as setting forth all the solutions to the problem.

III. Olson requires the stimulatory protein stationed on the formerly inhibitory site to institute a directed pattern rather than random nerve growth.

Furthermore, the rejections based on *Olson* would also destroy the third key feature of *Olson*, namely directed rather than random nerve regeneration. *Olson* discloses that a major advantage of the amphibody-based methods set forth therein is that it "avoids the stochastic or random axonal growth that the previously known non-specific coadministration methods may cause. Instead, the present claimed neuromodulators put the injured axons back on track by providing guidance and enforcing direction of their growth and/or elongation" and instead enforces "the direction of their growth and/or elongation" by its anchored neurotrophic factor. See *id.* at 7:1-4; also see 9:20-26.

Olson requires that the amphibody achieve a "vital turnabout change of milieu by on the spot neutralizing [of] negative cues and in situ exposing positive modulators of axonal growth in a 'sugarcoat' fashion." See *Olson* at 19:10-14. According to *Olson*, it is not enough that a formerly inhibitory region become merely neutral. See *id.* at 19:17-18. As stated in *Olson*, a stimulatory moiety should work "precisely on the spot of the previously exposed inhibitory sites, turning a negative environment into a positive one rather than a neutral one. This is the essence of molecular guising...." See *id.* at 19:19-26. As stated above, *Olson* therefore teaches away from turning the inhibitory site into a merely neutral site and emphasizes turning the inhibitory

site into a stimulatory site ("precisely on the spot") to further its purpose of directed axonal growth.

The *Olson* reference teaches and/or leads away from the present claimed invention in which the first polypeptide sequence "degrades a nerve growth-inhibiting substance." In marked contrast to *Olson*, with the claimed invention the inhibitory sites are destroyed by the first polypeptide sequence, thereby allowing the chimeric protein to then freely move around and act where it is needed.

Furthermore, the deficiencies of *Olson* are not solved in any of the other cited references. The claimed elements of the present invention are not found in the cited art when viewed alone or in combination. The Office argues that *Olson* does not teach or suggest that keeping the structure of the inhibitory molecule intact is important. Applicant respectfully disagrees. If the inhibitory molecule were to be degraded, the amphibody could not dock and cap, and provide a "chemoattractant railway." See *Olson* at pg. 20, lns. 1-4.

Yick and *Zuo* were cited along with *Olson* for each of the claims. The Office's rationale appears to be that because some regeneration was shown in *Yick* or *Zuo* that this occurrence means that there were no accompanying negative effects (i.e., side effects). However, Applicant notes that *Olson* cites *Dou* and *Levine* at page 26, lines 16-17 regarding the inhibitory effects of proteoglycans. Of note, *Dou* and *Levine* state that inhibitory effects of digested proteoglycans (e.g. NG2 digested with chondroitinase ABC) are "quantitatively identical to that of the intact proteoglycan" (see *Dou* and *Levine*, 1994: Abstract, p. 7622). Without limitation, the *Dou* and *Levine* disclosure would not motivate one of skill in the art to digest proteoglycans if the remaining core were equally inhibitory. Moreover, even if the asserted interpretation of *Yick* and *Zuo* were true, this still would not alter the fact that requisite teaching of the primary reference cannot be disregarded such that the intended function and use of *Olson* is destroyed.

As stated above, *Olson* discloses that a major advantage and the principle of operation of the amphibody is that the anti-end of the amphibody docks and caps the inhibitory molecule while the stimulatory end of the amphibody simultaneously presents a guide for the growing neuron to advance. For example, see *Olson* at pg. 20, lns. 1-4, which refers to the stimulatory

end of the amphibody as having the ability to introduce the growing nerve tip to a "chemoattractant railway." FIG. 2 of *Olson* further illustrates this "chemoattractant railway." See also *Olson* at pg 21, lns. 6-7. In the amphibodies of *Olson*, the growth attractant function is not merely an optional embodiment, it is stated to be how amphibodies function. See *Olson* at pg. 21, lns. 1-2.

In contrast, the claimed chimeric protein does not dock and cap the inhibitory molecule but instead destroys it. The requisite anchoring and directed growth aspects of the *Olson* teach away from the degradation of inhibitory substances function encompassed by the present invention as well as the corresponding pattern of "non-directed" growth that can ensure upon use of the present invention.

Yick or *Zuo* were also cited along with *Olson*. Neither of these references, nor a combination thereof, solves the deficiencies of *Olson*. Nothing in these references indicates that one should destroy the binding and anchoring function of *Olson*. Moreover, the cited references fail to teach or suggest a chimeric protein comprising a first polypeptide sequence selected from the group consisting of chondroitinases, hyaluronidases, and matrix metalloproteinases and a second polypeptide sequence which possesses regenerating activity for neural cells.

For the reasons stated above, *Olson*, *Yick* and/or *Zuo*, either alone or in combination, do not render obvious independent claim 27. Elements of the this independent claim are not present in the cited art, and because claims 28-35 depend from claim 27, claims 28-35 are also nonobvious over the cited references. Accordingly, Applicant respectfully requests that the rejections associated with claims 27-35 be withdrawn.

Rejection of Claim 32

Claim 32 is rejected under 35 U.S.C. § 103(a) as being obvious over *Olson* in view of *Yick* or *Zuo* further in view of *Gearing*. Dependent claim 32 recites that the linker of independent claim 27 is an Fc region of an immunoglobulin.

In addition to the reasons discussed above regarding *Olson*, *Yick* and *Zuo*, Applicants respectfully submit that claim 32 is nonobvious over *Olson*, *Yick*, *Zuo* and *Gearing*, either alone

or in combination. The addition of Gearing to the other cited references, does nothing to resolve the fact that it could not have been obvious to destroy the intended function of the primary *Olson* reference.

The Office acknowledges that *Olson*, *Yick* and *Zuo* do not disclose the use of an immunoglobulin Fc portion as the peptide linker between the two portions of the chimeric protein. However, the Office asserts that *Gearing* teaches a fusion protein composed of two subunits connected through an immunoglobulin Fc peptide linker. See *Gearing* at pg. 8, lns. 17-43. However, *Gearing* does not disclose an immunoglobulin Fc peptide linker bound to a regenerative polypeptide component.

Moreover, these cited references fail to teach or suggest a chimeric protein comprising a first polypeptide sequence which degrades a nerve growth-inhibiting substance and a second polypeptide sequence which possesses growth-promoting activity for neural cells, where these two polypeptide sequences are linked by a peptide linker comprising the Fc portion of an immunoglobulin.

For the reasons stated above, *Olson*, *Yick*, *Zuo* and *Gearing*, either alone or in combination, do not render claim 32 obvious. Accordingly, Applicant respectfully requests that the rejection associated with claim 32 be withdrawn.

All of the stated grounds of rejection have been properly traversed, accommodated or rendered moot. Applicant, therefore, respectfully requests that the Examiner reconsider and withdraw all presently outstanding rejections. There being no other rejections, Applicant respectfully requests that the current application be immediately allowed and passed to issue.

If the Examiner believes for any reason that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned directly.

CONCLUSION

The Commissioner is hereby authorized to charge any additional fees which may be required for this submission, or credit any overpayment, to Deposit Account No. 50-0436.

Respectfully submitted,
PEPPER HAMILTON LLP

N. Nicole Endejann
Registration No. 50,229

BNY Mellon Center, 50th Floor
500 Grant Street
Pittsburgh, PA 15219-2505
Telephone: (412) 454-5869
Facsimile: (412) 281-0717
Date: September 30, 2010